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Capecitabine as first-line treatment in colorectal cancer: pooled data from two large, phase III trials

C. Twelves*on behalf of the Xeloda Colorectal Cancer Group

Alexander Stone Building, CRC Department of Medical Oncology, Switchback Road, Garscube Estate, Bearsden, Glasgow G61 1BD, UK

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Abstract

The oral, tumour-selective fluoropyrimidine capecitabine represents a major new strategy for the treatment of colorectal cancer. Pooled results from two large, multicentre, open-label, phase III studies comparing oral capecitabine (1250 mg/m^2 twice daily for 14 days every 3 weeks) with the Mayo Clinic regimen (5-fluorouracil [5-FU] 425 mg/m^2 plus leucovorin 20 mg/m^2 days 1–5, every 4 weeks) provide information on over 1200 patients receiving first-line chemotherapy for metastatic colorectal cancer. Analysis of all randomised patients demonstrated a significantly superior overall response rate as assessed by the investigator for capecitabine compared with 5-FU/leucovorin (25.7% versus 16.7%, $P<0.0002$), reinforcing the individual trial results. Median time to disease progression, overall survival and duration of response were equivalent in the two treatment groups. Furthermore, capecitabine showed a superior safety profile compared with 5-FU/leucovorin, with a significantly lower incidence ($P<0.001$) of diarrhoea, stomatitis, nausea and alopecia, together with a reduced treatment-related hospitalisation rate. In addition, the incidence of neutropenic fever/sepsis was significantly lower in patients receiving capecitabine.

Keywords: Capecitabine; Efficacy; Colorectal cancer; Clinical trial; Safety; Fluoropyrimidines

1. Introduction

Capecitabine is an oral, enzymatically-activated fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FU) preferentially at the tumour site by a sequential three enzyme pathway. Its tumour-selective mechanism of activation results in higher concentrations of 5-FU in malignant cells compared with normal tissues and plasma [1]. As such, capecitabine represents the first in a new class of oral agents, providing an exciting strategy in the first-line treatment for metastatic colorectal cancer.

The clinical development programme for capecitabine in colorectal cancer encompasses phase I studies in both Europe and the USA [2–4]; a randomised, phase II trial [5]; two large, randomised, multicentre, open-label, phase III studies [6,7] and an ongoing phase IIIb adjuvant trial. Initial phase I trials showed capecitabine was well absorbed and well tolerated. In phase II trials, capecitabine was active against colorectal and breast cancer at a dose of 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period [5,8–11].

The primary focus of the capecitabine trial programme in colorectal cancer was two multicentre, open-label, phase III studies, which have been conducted to compare capecitabine with 5-FU/leucovorin (Mayo Clinic regimen) as first-line treatment for metastatic colorectal cancer [6,7]. The studies used identical protocols and conduct, and an integrated analysis of all data was prospectively planned, thus providing information on a population of more than 1200 patients. One study was conducted in Europe, Australia and Asia and the other was conducted in the USA, Brazil and Mexico. The pooled data from all randomised patients are presented here.

In addition, a trial (the Xeloda Adjuvant Chemotherapy Trial [X-ACT] study) aiming to recruit 1956 patients with Dukes' C colon cancer in the adjuvant setting completed recruitment in September 2001. The primary objective of this study is to demonstrate that capecitabine monotherapy is at least as effective as the 5-FU/leucovorin Mayo Clinic regimen in terms of disease-free survival. Further details of this study are provided in the review by Wilke elsewhere in this supplement [12].

* Tel.: +44-141-211-1712; fax: +44-141-211-1869.
E-mail address: c.twelves@beatson.gla.ac.uk (C. Twelves).

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2. Patients and methods

2.1. Aims and objectives

Two randomised, multicentre, open-label, phase III studies have been conducted to compare oral capecitabine (1250 mg/m^2 twice daily for 14 days, every 3 weeks) with intravenous (i.v.) bolus 5-FU/leucovorin (Mayo Clinic regimen: 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 days 1–5, every 4 weeks) as first-line treatment for metastatic colorectal cancer. The two studies used identical protocols and conduct, with the primary objective of establishing that oral capecitabine achieves a response rate at least equivalent to i.v. 5-FU/leucovorin in patients with previously untreated metastatic colorectal cancer. Secondary objectives were to compare additional efficacy parameters (time to disease progression, overall survival, duration of response and time to first response), safety profile and medical care utilisation during treatment.

2.2. Treatment and efficacy evaluation

Patients were randomised to receive either oral capecitabine ($n = 603$) or i.v. 5-FU/leucovorin ($n = 604$). All patients were included in the efficacy analysis. Investigators assessed tumour response based on standard World Health Organization criteria. In addition, an Independent Review Committee (IRC), consisting of a panel of radiologists who were blind to study treatment, clinical condition of the patient and investigator's assessment, assessed tumour responses solely on the basis of X-ray or scan imaging.

Table 1
Demographics

	Capecitabine ($n = 603$)	5-FU/leucovorin ($n = 604$)
Male/female (%)	60/40	61/39
Age (years): median (range)	64 (23–86)	63 (24–87)
KPS (%): mean (range)	89 (70–100)	89 (70–100)
Colon/rectal cancer (%)	70/30	71/29
Predominant metastatic site		
Liver (%)	77	77
Lung (%)	12	14
Prior 5-FU-based adjuvant treatment (%)	24	26

KPS, Karnofsky Performance Status; 5-FU, 5-fluorouracil.

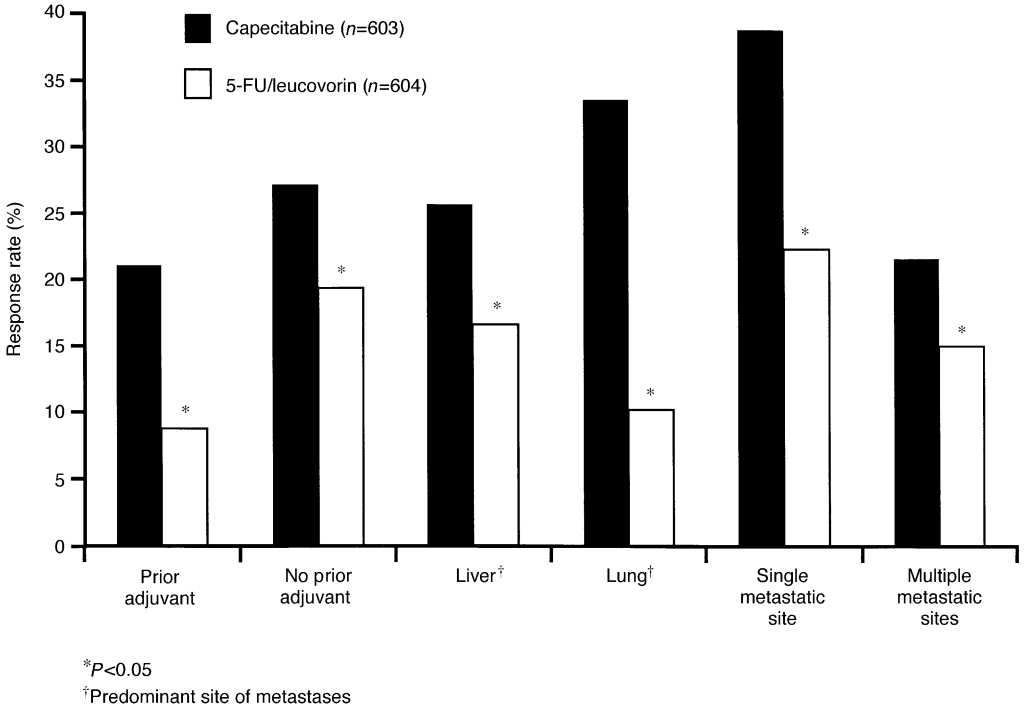

Fig. 1. Response rates to capecitabine or 5-fluorouracil (5-FU)/leucovorin according to patient subpopulation. Reproduced with permission from The Oncologist 2001:6(suppl. 4):3–11 ©AlphaMed Press 1083–7159.

2.3. Safety evaluation

All patients who received at least one dose of the study drug (596 patients in the capecitabine arm; 593 patients in the 5-FU/leucovorin arm) were included in the safety analysis. Adverse events were graded according to the strict criteria of the 1994 National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC). Hand–foot syndrome was graded according to clinical and functional domains, as in phase II studies [5,8].

Haematological or chemical laboratory abnormalities were recorded throughout the study. The number of hospitalisations and percentage of patients requiring hospitalisation as a result of side-effects were also recorded, together with any dose reductions required.

3. Results

3.1. Patient demographics

Patient demographics were very similar in the two treatment groups (Table 1). The majority of patients had colon rather than rectal cancer and the liver was the predominant site of metastases. Approximately one-quarter of the patients in each of the treatment arms had received prior adjuvant 5-FU.

3.2. Tumour response

Results from the integrated analysis clearly demonstrated a significantly superior overall response rate (all

Table 2
Tumour response

	Capecitabine ($n=603$)	5-FU/leucovorin ($n=604$)	P value
Investigator			
PR + CR (%)	25.7	16.7	<0.0002
Stable disease (%)	47.8	52.2	
Independent Review Committee			
PR + CR (%)	22.4	13.2	<0.0001
Stable disease (%)	52.9	57.6	

PR, partial response; CR, complete response; 5-FU, 5-fluorouracil.

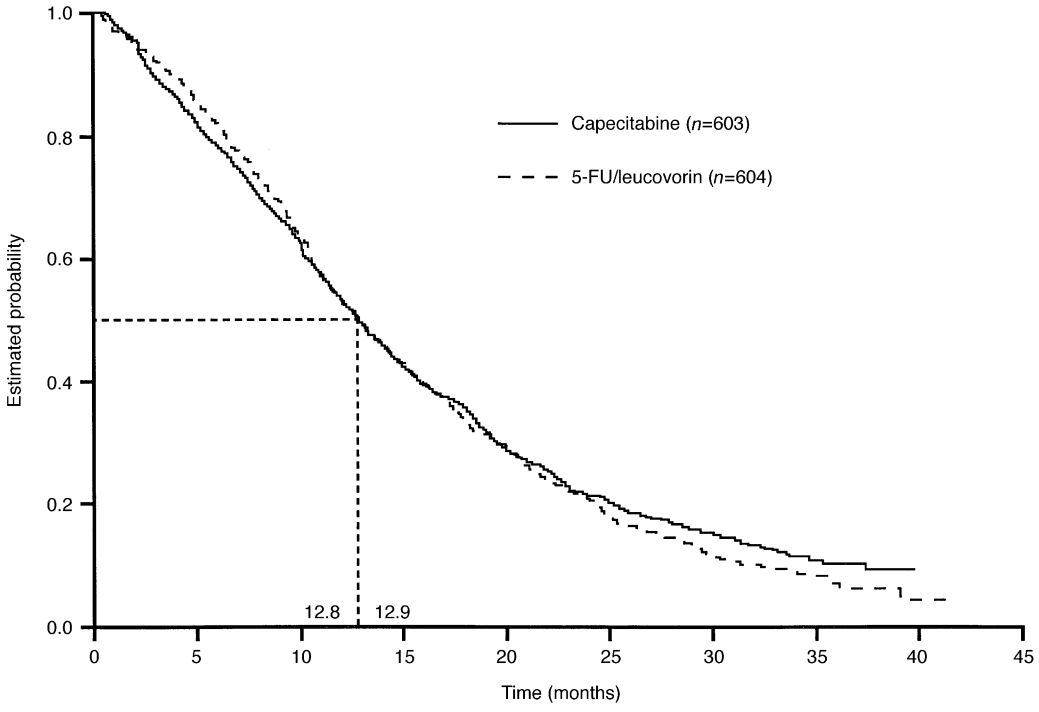

Fig. 2. Overall survival with capecitabine or 5-fluorouracil (5-FU)/leucovorin.

randomised population, investigator assessment) in the capecitabine arm compared with the 5-FU/leucovorin arm (25.7% versus 16.7%, $P < 0.0002$; two-sided χ^2-test with Schouten correction) (Table 2). This result was confirmed by the IRC assessment (22.4% versus 13.2%, respectively, $P < 0.0001$; two-sided χ^2-test with Schouten correction). Analysis of the data according to baseline characteristics (prior adjuvant treatment, predominant site of metastases and number of metastatic sites) in each case revealed a consistently and significantly higher response rate in favour of the capecitabine treatment ($P < 0.05$; two-sided χ^2-test with Schouten correction) (Fig. 1). Of note, in patients who had received prior adjuvant treatment the response rate with capecitabine was 21.1% compared with only 9.0% in patients treated with 5-FU/leucovorin. The 'tumour control rate' (complete [CR] or partial response [PR] or stable disease [SD]) was 73.6% with capecitabine versus 68.9% with 5-FU/leucovorin ($P = 0.07$).

Capecitabine demonstrated equivalent efficacy to 5-FU/leucovorin for all secondary endpoints of the study. Median time to disease progression was 4.6 months for capecitabine (95% confidence interval [CI]:4.3–5.3) compared with 4.7 months in the 5-FU/leucovorin group (95% CI:4.3–5.4). The median survival was 12.9 months in the capecitabine group and 12.8 months in the 5-FU/leucovorin group (hazard ratio = 0.96, 95% CI: 0.85–1.08) (Fig. 2). Median time to treatment failure was also similar (4.2 months with capecitabine versus 3.6 months with 5-FU/leucovorin). In addition, response to treatment occurred at least as early in patients treated with capecitabine compared with patients in the 5-FU/leucovorin arm (median time to response: 1.7 versus 2.4 months, respectively).

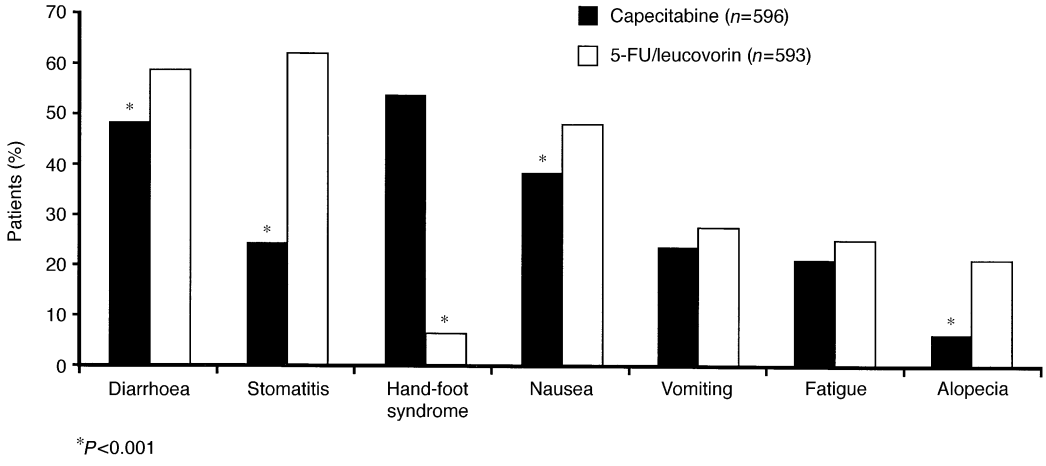

Fig. 3. Most common treatment-related adverse events following treatment with capecitabine or 5-fluorouracil (5-FU)/leucovorin. Reproduced with permission from The Oncologist 2001:6(suppl. 4):3–11 ©AlphaMed Press 1083–7159.

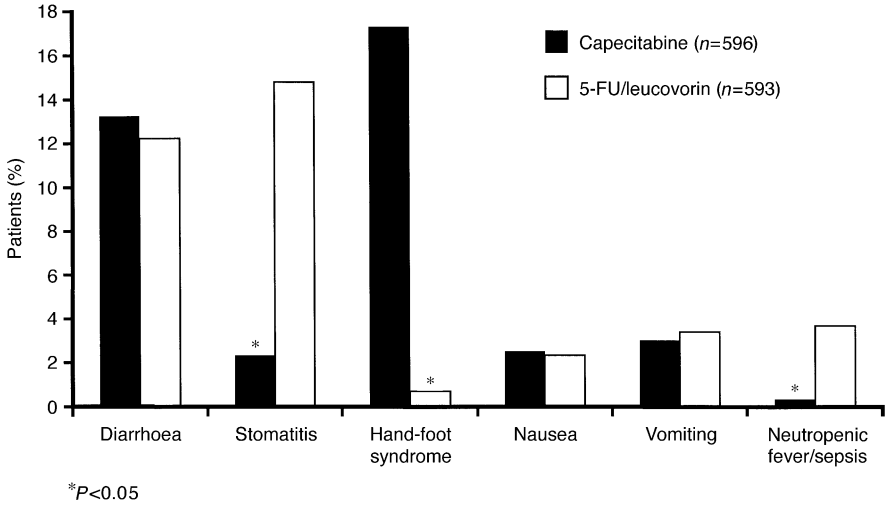

Fig. 4. Most common grade 3/4 treatment-related adverse events following treatment with capecitabine or 5-fluorouracil (5-FU)/leucovorin. Reproduced with permission from The Oncologist 2001:6(suppl. 4):3–11 ©AlphaMed Press 1083–7159.

3.3. Safety

A significantly ($P<0.001$) lower incidence of the following side-effects commonly associated with fluoropyrimidine treatment was observed with capecitabine compared with 5-FU/leucovorin: diarrhoea (48% versus 58%), stomatitis (24% versus 62%), nausea (38% versus 47%) and alopecia (6% versus 21%) (two-sided χ^2-test with Schouten correction) (Fig. 3). The incidence of vomiting and fatigue was similar in both treatment groups. The only adverse event which occurred more frequently with capecitabine than 5-FU/leucovorin was hand–foot syndrome affecting the palms and soles (all grades: 53% versus 6%; grade 3: 17% versus 1%; grade 4: not applicable). This was, however, easily managed by interrupting the treatment and, if necessary, a dose reduction. Hand–foot syndrome rarely led to hospitalisation (0.3%) or withdrawal from treatment (1.7%). Of note, grade 3/4 stomatitis occurred in only approximately 2% of patients receiving capecitabine, but was a major side-effect of 5-FU/leucovorin treatment (15%, $P<0.0001$) (Fig. 4).

3.4. Laboratory abnormalities

Grade 3 or 4 neutropenia was significantly more common in the 5-FU/leucovorin group compared with patients receiving capecitabine (21.1% versus 2.2%), resulting in a significantly higher incidence of neutropenic fever and sepsis and more associated hospitalisations. Biochemical parameters were generally similar between the treatment groups, although the incidence of hyperbilirubinaemia was higher in patients receiving capecitabine. A higher percentage of capecitabine-treated patients developed total bilirubin levels >1.5 and $\leqslant 3$ times the upper limit of normal (grade 3, 18.3% versus 3.3%, respectively; $P<0.0001$). Bilirubin concentrations >3 times the upper limit of normal (grade 4 hyperbilirubinaemia) occurred at a similar rate in both treatment groups (4.5% versus 2.5%, respectively; $P=0.07$). Hyperbilirubinaemia affected almost exclusively the indirect bilirubin and tended to be an asymptomatic isolated laboratory abnormality. It was rarely associated with a significant elevation of serum transaminases (0.7% of the capecitabine groups compared with 0.5% of the 5-FU/leucovorin group), and disturbances in liver biochemistry were not cumulative.

3.5. Treatment-related hospitalisations and dose reductions

Hospitalisation for treatment-related adverse events was significantly less frequent in the capecitabine group compared with the 5-FU/leucovorin group (11.6% versus 18.0%, respectively; $P=0.002$). Furthermore, capecitabine resulted in significantly fewer hospitalisations (76 versus 113, $P<0.005$) than 5-FU/leucovorin. Hospitalisations for key adverse events such as diarrhoea, nausea and vomiting were generally similar with the two treatments. However, a total of 21 patients receiving 5-FU/leucovorin required hospitalisation for stomatitis compared with only one patient treated with capecitabine (3.5% versus 0.2% respectively, $P<0.001$). Similarly, neutropenic fever/sepsis resulted in hospitalisation more frequently in the 5-FU/leucovorin-treatment arm than in the capecitabine arm (2.9% versus 0.2%, respectively, $P<0.001$). In comparison, hand–foot syndrome caused hospitalisation in only two capecitabine-treated patients (0.3%) and was successfully managed by treatment interruption and dose reduction, where necessary. In addition, patients receiving capecitabine require substantially fewer visits for treatment administration compared with those treated with Mayo Clinic regimen (four versus 15 visits in a 12-week treatment period).

Dose reductions for adverse events occurred less frequently with capecitabine than with 5-FU/leucovorin (34% versus 42%, respectively; $P<0.004$). Furthermore, dose reductions for adverse events occurred later in patients receiving capecitabine than in patients treated with 5-FU/leucovorin, with a median time to dose reduction of 2.5 versus 1.2 months. Therefore, among patients whose disease progresses, those receiving capecitabine are less likely to experience toxicities than patients receiving the Mayo Clinic regimen. Treatment-related mortality was low in both arms at a rate of 1% in each group.

4. Conclusions

Capecitabine is a novel, oral, tumour-selective fluoropyrimidine carbamate. Pooled results from two large, randomised, phase III studies have shown that capecitabine is at least as effective as i.v. bolus 5-FU/leucovorin (Mayo Clinic regimen). Oral capecitabine produced superior ($P<0.0002$) response rates with equivalent time to disease progression and overall survival. In addition, capecitabine was better tolerated than 5-FU. Capecitabine is, therefore, an effective, well-tolerated, convenient treatment for patients with colorectal cancer. In common with other effective fluoropyrimidine regimens, capecitabine did not improve median survival [13,14] There is, therefore, general agreement among oncologists that to make a positive impact on survival, the most active fluoropyrimidine regimens should be combined with agents such as irinotecan and oxaliplatin in patients suitable for combination therapy. These approaches will be discussed further in the article by Wilke in this supplement [12].

Capecitabine was better tolerated than the Mayo Clinic regimen, resulting in a significantly lower incidence of stomatitis, diarrhoea, nausea and alopecia. The incidence of grade 3/4 stomatitis and neutropenic fever/

sepsis leading to hospitalisation was also significantly lower with capecitabine than with 5-FU/leucovorin. In addition to the less frequent treatment administration visits for capecitabine, the overall hospitalisation rate for patients receiving capecitabine was significantly lower than in those receiving 5-FU/leucovorin. Capecitabine treatment resulted in a higher incidence of hand–foot syndrome compared with 5-FU/leucovorin, but this localised, cutaneous toxicity rarely led to hospitalisation or treatment withdrawal and was easily managed by treatment interruption and, if necessary, dose adjustment and patient counselling.

Most patients prefer an orally administered therapy to i.v. treatment [15,16]. Oral agents potentially permit convenient, patient-orientated therapy and avoid complications associated with i.v. drug administration. However, neither patients nor oncologists are prepared to sacrifice efficacy for the sake of convenience, which makes the efficacy and tolerability of capecitabine seen in these large, randomised trials extremely compelling.

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